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STUDY ON THE EFFECT OF TILETAMINE-ZOLAZEPAM AND KETOFOL IN CONJUCTION WITH GLYCOPYRROLATE, PENTAZOCINE-LACTATE AND MIDAZOLAM ON CLINICO-PHYSIOLOGICAL PARAMETERS IN DOGS.

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ABSTRACT

Current research was carried out for studies on the comparative evaluation of ketofol and tiletamine-zolazepam in conjunction with glycopyrrolate, pentazocine-lactate and midazolam for surgical intervention in dogs. The animals were separated into two distinct groups, having six animals each. Dogs were premedicated in both groups with glycopyrrolate @0.01 mg/kg b.wt I/M. and after 05 minutes pentazocine lactate @ 2 mg /kg bwt I/V and midazolam @ 0.5 mg /kg b.wt I/V. In group I animals were induced and maintained with tiletamine-zolazepam @ 6.5 mg/kg b.wt I/V and in group II, animal were induced and maintained with ketofol @ 4 mg/kg b.wt I/V. Heart rate after administration of anaesthesia increased non-significanlty in group I and II. Respiration rate increased significantly after induction in group I and non-significantly in group II. Non-significant decrease in rectal temperature after induction was observed in both the groups. SpO2% decreased significantly in group I and II. An initial increase in MAP was observed in group I and II.

Keywords: Clinical-physiological parameters, Dog, glycopyrrolate, ketofol, midazolam, pentazocine-lactate, tiletamine-zolazepam,

INTRODUCTION

Anesthesia is an indispensable prerequisite for any surgical interventions which demands humane handling and technical efficiency. It is the prime force that helps surgeons to execute their skill and expertise with utmost accuracy. An excellent anaesthetic agents is expected to produce reversible unconsciousness, analgesia, immobility and muscle relaxation with minimal side effects along with smooth induction and recovery (Okwudili *et al*., 2014).

Tiletamine–zolazepam is a combination of dissociative anaesthesia and benzodiazepine in the ratio of 1:1 (Plumb, 2018). Tiletamine possess peculiar characteristic of dissociative anaesthesia i.e.

convulsions and catalepsy. However, these shortcomings are taken care by zolazepam which acts as an anti-convulsant agent (Ferrari *et al*., 2005).

Ketofol is an admixture of ketamine and propofol in the ratio of 1:1 and its use are widespread for routine sedation (Donnelly *et al.,* 2008). Addition of ketamine to propofol boosts unprompted breathing, improves hemodynamic parameters, preserves airways, enhances analgesia and produce rapid recovery (Saeed, 2011).

Pre-anaesthetic are administered to animal for smooth induction maintenance and recovery. It reduces anaesthetic dose and eliminate the side effects of these agents on vital organs (Liptak *et al.,* 2012).

Glycopyrrolate is a recombinant quaternary ammonium molecule that is anticholinergic and has no central effects. It is around five times as effective as atropine and has a strong, long-lasting anti-sialagogue action (Hall *et al.,* 2014).

Pentazocine is the derivative of benzomorphan. The agonistic activity of Kappa-1 opioid receptors is responsible for analgesic effect of pentazocine and its sedative properties facilitate its usage as a pre-anaesthetic, when combined with other medications (Hardman *et al.,* 1996).

Midazolam is benzodiazepine derivative and short acting in nature that is commonly used as an adjuvant for anesthesia, sedation and anxiolysis. It has a short elimination half-life, considerable anterograde amnesia, low hemodynamic effects at sedation doses, slight respiratory depression and anxiety reduction (Sun *et al.,* 2008).

Material methods

The work was conducted on 12 dogs brought to Veterinary Clinical Complex, Rewa for surgical intervention. Irrespective of age, sex and breed these animals were randomly divided in two groups having six animals each. All the animals were kept off feed for 12 to 18 hours and deprived of water for 08 to 12 hours prior to anaesthesia. In both the groups, dogs were pre-anaesthetized with glycopyrrolate @ 0.01 mg/kg b.wt. I/M followed by pentazocine lactate @ 2 mg /kg b.wt. I/V and midazolam @ 0.5 mg /kg b.wt. I/V after 5 minutes. Anaesthesia was induced by tiletamine-zolazepam @ 6.5 mg/kg b.wt. I/V and Ketofol @ 4mg/kg b.wt. I/V till effect after 10 minutes in group I and II respectively. Maintenance of anaesthesia in group I and II was done by tiletamine-zolazepam and ketofol I/V as and when required. Clinico-physiological parameters i.e. Heart rate (beats/min), respiration rate (breaths/min), rectal temperature (ºF), saturation of peripheral oxygen (%), mean arterial pressure (mm Hg) were recorded before pre-anaesthesia (0 minutes), 15 minutes (base-line) i.e. after pre-anaesthetic administration and at 30, 45, 60, 75 and 90 minutes interval after administration of anaesthetic agents.

Results and discussion

Clinicophysiological parameters of both the groups are mentioned in table 01

Table 01: Mean values of different clinical parameters

Time	Heart Rate		Respiration Rate		Rectal Temperature		SpO_2 %		Mean Arterial Pressure	
Group	**I**	**II**	**I**	**II**	**I**	**II**	**I**	**II**	**I**	**II**
Before pre-anaesthesia	119.66^{b}±2.82	121.33±2.06	26.16^{a}±0.90	24.66^{a}±0.88	101.86^{a}±0.22	101.02±0.38	97.00^{a}±0.36	96.83^{abc}±0.16	107.83^{b}±1.97	108.66^{b}±1.14
15 Minutes	118.50^{b}±2.84	120.00±2.01	25.00^{a}±0.85	23.66^{abc}±0.88	101.63^{ab}±0.21	100.71±0.40	96.16^{abc}±0.47	96.33^{c}±0.21	107.16^{b}±1.90	108.16^{b}±0.83
30 Minutes	129.83^{Aa}±2.53	123.50^{AB}±2.59	21.66^{b}±1.05	21.33^{c}±0.76	101.40^{ab}±0.23	100.48±0.42	94.50^{Bd}±0.22	95.50^{Ad}±0.22	115.16^{Aa}±1.93	110.16^{ABab}±0.98
45 Minutes	126.16^{ab}±2.48	126.33±2.44	19.33^{Bbc}±0.88	22.00^{Abc}±0.68	101.00^{bc}±0.22	100.73±0.44	95.16^{Bcd}±0.47	95.33^{Bd}±0.21	112.16^{ab}±1.79	112.50^{ab}±0.71
60 Minutes	124.66^{ab}±2.34	123.66±2.61	18.50^{Bc}±0.76	22.50^{Aabc}±0.67	100.68^{cd}±0.24	101.05±0.43	95.33^{Bcd}±0.21	96.50^{Abc}±0.22	109.33^{b}±1.70	110.00^{b}±0.89
75 Minutes	122.83^{ab}±2.37	122.33±2.81	20.33^{Bbc}±0.76	23.33^{Aabc}±0.61	100.25^{Bde}±0.23	101.33^{A}±0.46	95.66^{Bbc}±0.42	97.16^{Aab}±0.30	108.33^{b}±1.70	109.50^{b}±0.61
90 Minutes	121.33^{b}±2.47	121.16±2.97	21.50^{Bb}±0.76	24.00^{Aab}±0.68	99.76^{Be}±0.24	101.55^{A}±0.42	96.50^{Bab}±0.22	97.50^{Aa}±0.22	106.50^{b}±1.78	108.33^{b}±0.33

Means with different superscripts small letter (a, b, c) in a column and capital letter (A, B, C) in a row differ significantly ($p \leq 0.05$)

Decrease in heart rate at initial interval after administration of midazolam was observed in both the groups at 15 minutes time interval as it depress the CNS activity. Midazolam exerts their primary effects by increasing activity of endogenous gamma amino butyric acid (GABA), an inhibitory neurotransmitter in the brain (Thomas and Lerche 2003). Heart rate in group I increased significantly at 30 minutes and non-significantly at 45 minutes from the base line value. Initial increase in heart rate after tiletamine- zolazepam administration could be explained by the observation of Hall *et al.* (2014), Hampton *et al.* (2019) and Pireira *et al.* (2019) who attributed it to sympathomimetic activity of tiletamine, which increase heart rate by stimulation of sinus node a characteristic exhibited by dissociative agents. The heart rate in Group II increased non-significantly at 30 and 45 minutes from the base line value, the initial increase in heart rate could be explained by the findings of Kumar *et al.* (2014), who found an increase in heart rate after ketofol administration and attributed it to enhanced sympathetic activation linked to unconsciousness or a compensatory reaction to lower blood pressure through arterial vasodilation. Increase in heart rate after ketofol administration in present study might be due to combination of ketamine and propofol. Although propofol decreases myocardial contractibility its activity is slightly masked by the increased sympathetic efferent activity of ketamine.

In group I a significant decrease in respiration rate was observed following administration of tiletamine-zolazepam combination in dogs. Valadao and Pacchini (2001) mentioned that the combination of tiletamine and zolazepam causes transient respiratory depression following its intravenous administration. Furthermore, it results in the development of an apneustic respiratory pattern, which is distinguished by deep breathing that occurs irregularly and with prolonged pauses. In group II a non-significant decrease in respiration rate was noted at 30 minutes from baseline value. The decrease in respiration rate after ketofol administration in present study could be explained by combined hypothesis of Haskins *et al.* (1985) and Goodman *et al.* (1987). Haskins *et al.* (1985) mentioned that decrease in respiration after ketamine administration might be due to respiratory depressant effect of ketamine. Goodman *et al.* (1987) mentioned that propofol causes depression of central inspiratory drive and the ventilatory response to arterial CO_2 tension. Ketofol is a mixture of above two drugs and hence, a combined effect of both these drugs might have caused an initial decrease in respiration rate.

Rectal temperature in group I decreased non-significantly at 30 and 45 minutes time interval in comparison to baseline value, the decrease in rectal temperature in present study could be explained by the findings of Lu *et al.* (2014) who found decrease in rectal temperature after administration of tiletamine-zolazepam combination and attributed it to generalized somnolence, reduced metabolic rate and muscle relaxation caused by this combination. Rectal temperature in group II decreased non-significantly at 30 and 45 minutes time interval from base line value which was followed by non-significant increase till the end of observation period. Non-significant decrease in initial stage and nonsignificant increase in rectal temperature at later stage of observation after ketofol administration could be explained by the findings of Shinde *et al.* (2018) who observed an insignificant decrease in rectal temperature following ketofol injection and attributed it to hypotensive activity of propofol, which lowers peripheral blood pressure and

increases stress during surgical intervention. However, the ketamine component of ketofol stimulates the circulatory system, counteracting the hypotensive impact of propofol allowing the body temperature to remain stable during anesthesia.

SpO_2 in group I decreased significantly at 30 minutes time interval in comparison to baseline value, followed by a non-significant increase till the end of observation period, the decrease in respiratory rate in initial stage of present study could be explained by the hypothesis of Thomas and Lerche (2003) who documented that the respiratory depressive effect of tiletamine-zolazepam combination becomes significant when it is combined with other anesthetics or sedatives. SpO_2 in group II decreased significantly at 30 and 45 minutes time interval in comparison to base line value, which was followed by significant increase till the end of observation period. Lumb *et al.* (2007) described that propofol and ketamine lowers the brain metabolic activity and increases the effects of the inhibitory neurotransmitter GABA, which lowers SpO2 and results in depression.

In group I a significant increase in MAP was observed at 30 minutes time interval in comparison to baseline which was succeeded by non-significant decrease till the end of observation period in comparison to base line value. Hall *et al.* (2014) opined that tiletamine-zolazepam produces tachycardia along with a modest elevation in blood pressure. The positive ionotropic impact of dissociative anesthesia on the heart is responsible for of the increase in MAP in initial stage of observation. In group II a non-significant increase in MAP was observed at 30 minutes time interval and significant increase at 45 minutes in comparison to base line value that was succeeded by non-significant decrease till the end of observation period. Butola and singh (2003) and Rastabi *et al.* (2018) observed increase in MAP after administration of ketofol and attributed it to an increase in arterial blood pressure. Ketofol has a selective positive ionotropic effect on the heart muscles or reflexogenic alterations in the autonomic nervous system, which raises the heart rate and increases MAP values despite becoming significantly different.

Conclusions

From the above discussion it could be concluded that glycopyrrolate, pentazocine and midazolam acts as an excellent premedication agents. Tiletamine-zolazepam and ketofol could be used safely with the above premedication without any marked physiological complications.

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